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REMARKS

Below are presented detailed remarks addressing each objection/rejection raised filed in the office action dated January 24, 2005.

Claim Rejections - 35 U.S.C. § 102

1) Rejections based on Dorner and Interpretation of "shed" blood by dictionary definition

In response to the continued rejection of claims 1-3, 5-10 and 21-23 as anticipated by Dorner et al., "Efficacy of leucocyte-poor red blood cell suspensions prepared by sedimentation in hydroxyethyl starch", Transfusion 15 (5) : 439-48 (1975), applicants request reconsideration. In particular, it is requested that reconsideration be given of the significance of the claim term "shed" in view of the recent en banc U.S. Court of Appeals for the Federal Circuit Decision in *Phillips v. AWH Corporation, No. 03-1269, 1286 (Fed. Cir. July 12, 2005).*

In the previous response dated November 17, 2004, applicants amended claims 1, 5 and 6 to specify that the blood in the solution with the washing fluid and anticoagulant is shed blood. In the last action, the newly added claim term "shed" was interpreted by reference to a dictionary, from which a definition was provided as: "to cause to flow in a stream or fall in drops". In the action, it was reasoned that following the dictionary definition, all blood is considered "shed" and distinguishing prior art

methods based on the blood involved being "shed" failed to make the claims patentable.

Applicants traverse that rejection and request reconsideration of the definition of the term "shed" in light of the recent *Phillips* decision which states:

> "...the specification is the single best guide to the meaning of a disputed term and ...the specification acts as a dictionary when it expressly defines terms used in the claim or when it defines terms by implication....Even when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents.
>
> The main problem with elevating the dictionary to such prominence is that it focuses inquiry on the abstract meaning of words rather than on the meaning of claim terms within the context of the patent. Properly viewed, the 'ordinary meaning' of the claim term is its meaning to the ordinary artisan after reading the entire patent. Yet heavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification." *Phillips 03-1269 -1286 slip opinion at pgs. 24-24 (citations omitted).*

In the specification of the present application, applicants state in the "*Technical Field*" at page 1, lines 6-7, that "This invention relates to methods for collecting,

washing, and returning blood to a patient." Several lines later in the specification, in the "*Background of the Invention*", it is stated: "... blood shed during surgery is often collected for the purpose of re-infusing the blood during surgery. The shed blood that has been collected may be washed before it is re-infused." In the *Summary of the Invention* at page 2 of the specification it is stated: "That is, in accordance with the invention, a cell salvage process wherein shed blood is combined with only inert anticoagulants and then mixed with a washing solution having a reagent, such as hetastarch, successfully separates red blood cells in a gravity sedimentation method.

The applicants' references to "shed" blood are consistently used to refer only to blood that is collected from a patient during surgery and re-infused back to the patient during the same procedure. Those references in the specification should indicate to one of ordinary skill in the art that the applicant intended "shed" blood to mean only such salvaged blood collected during a medical procedure as opposed to donated blood that may be stored and used later on a different person. Also, the above-referenced statements from the specification indicate that the invention pertains specifically to "shed" blood.

Finally, a known prior art patent listed in the background of the invention (U.S. Pat. No 5,282,982) on page one of applicants' specification also refers to "shed" blood in a manner consistent with the meaning developed in the present application. At column 1, lines 11-15 of the '982 patent it is stated: "Autotransfusion systems can often be employed during a surgical procedure to recover and wash shed blood for re-infusion into the patient when donated blood is scarce or unavailable or when there is

concern regarding the safety of the donated blood." That other patents in the field also refer to "shed" blood with the same meaning as do the applicants should serve as a confirmation of applicants' intended meaning and the meaning that one ordinary skill in the art would understand from the phrase.

It is reiterated that the methods of applicants' invention are directed to and are especially useful in blood salvage procedures in which blood is collected from the patient, washed and red blood cells returned right back to the patient. The blood collected from the patient for re-infusion during such procedures is referred to as shed blood. Dorner mentions use only of stored blood or stored red blood cells in the methods discussed. Due to the likely metabolic differences between shed blood and stored blood, Dornrer's experiments can't be said to have direct relevance to applicants' invention.

Finally, regarding rejections based on Dorner, it was suggested in the last action that defining "shed" blood in the claims appeared to merely state an intended use, which is entitled to minimal patentable weight. Applicants point out that further defining blood to be "shed" serves to further define the method that is claimed. It is believed that no one before the applicants used an inert anticoagulant to process by sedimentation the shed blood and return it to a patient during a medical procedure.

Based on the holding of the recent *Phillips* case on claim interpretation and the previous amendments to the claims to define shed blood, Dorner should not be considered to anticipate claims 1-3, 5-10 and 21-23.

2) Rejections based on U.S. Pat. No. 4,765,899 (Wells et al.)

Applicants continue to traverse the rejection of claims 1, 4-6, 11 and 21-23 for all the reasons stated in the last response and request reconsideration in view of the following new comments. In the last action it was suggested that, in the prior art reference, ACD refers to anticoagulant-citrate-dextrose, wherein the anticoagulant is heparin. It was further suggested that ACD-A is not the same as ACD, making moot applicants' arguments that the specification stresses the avoidance of ACD-A in the process.

Applicants note that ACD is known as Acid Citrate Dextrose and is a solution containing citric acid, sodium citrate and dextrose (see excerpt from on-line Dorland's Medical Dictionary attached and highlighted). ACD is also known as Anticoagulant Citrate Dextrose solution (as noted in the action); however, the constituent parts of the solution are still citric acid, sodium citrate and dextrose (see Dorland's attached). The Anticoagulant in ACD does not refer to heparin. Heparin is a sulfated glycosaminoglycan of mixed polysaccharide nature that naturally occurs in the body (see Dorland's attached).

ACD-A is a form of ACD known as Solution A (see : *A Note in the Acid Citrate Dextrose Tube in the Present Usage* : Haema 2003; 6(3): 407-408, copy attached). The Solution A form of ACD comprises 22.0 g/l trisodium citrate, 8.0g/l citric acid, 24.5g/l dextrose. ACD-A contains the same constituent components as ACD (citric acid, sodium citrate and dextrose). Therefore, applicant's objectives stated in the specification of avoiding ACD-A are relevant to prior art teachings of ACD as well.

Furthermore, the examples provided in the '899 patent state that heparinized blood was placed into a container having ACD. The '899 patent does not appear to suggest that the Heparin was the only anticoagulant used in the examples or that ACD contains heparin.

Reconsideration of the rejections based on the '899 patent, in light of the information provided above and the arguments made in the last response, is requested.

Claim Rejections - 35 U.S.C. § 103

Applicants continue to traverse the obviousness rejections based on U.S. Pat No. 5,879,318 (Van der Heiden) in view of Dorner. Applicants maintain that rejections based on Van der Heiden are improper because the reference clearly uses centrifugation in the disclosed process. In the last action it was stated that using centrifugation to aid sedimentation is optional and that working examples or comparisons with the prior art to show unexpected results need to be demonstrated to overcome the obviousness rejection.

Applicants acknowledge that centrifugation devices are known for use in separating red blood cells from blood. However, blood component separation systems employing mechanized centrifuges are far more complex and costly than the gravity sedimentation system and method disclosed in the present application. The increased expense and complexity of the centrifuge-based systems is such that they are not readily interchangeable or optional means to separate blood components as was suggested in the action. In fact, it is envisioned that the system and method using

gravity sedimentation disclosed in the present application would be most useful in developing areas that do not have ready access to well-equipped facilities with powered devices such as centrifuge-based machines. Because the present method does not require a mechanized apparatus to carry out, it should be considered distinguishable from rather than interchangeable with methods that rely on such mechanized equipment.

Based on the foregoing remarks, reconsideration of the claim rejections is requested.

If there are any charges or any credits, please apply them to Deposit Account No. 50-3067.

Respectfully submitted,

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DORLAND'S MEDICAL DICTIONARY

<< Previous A-D | E-H | I-M | N-R | S-V | W-Z Next >>

A

acheirus — acidyl

acheirus **(achei·rus)** ([schwa]-ki′r[schwa]s) [L.] an individual exhibiting acheiria.

Achilles' bursa, jerk (reflex), tendon **(Achil·les' bur·sa, jerk (reflex), tendon)** ([schwa]-kil′[emacr]z) [Gr. *Achilleus* Greek hero, whose mother held him by the heel to dip him in the Styx] see bursa tendinis calcanei, triceps surae jerk, under *jerk*, and tendo calcaneus.

Achillini **(Ach·il·li·ni)** (ah″k[schwa]-le′ne) Alessandro (1463–1512). A celebrated Bolognese physician and philosopher who wrote on anatomy.

achillobursitis **(achil·lo·bur·si·tis)** ([schwa]-kil″o-b[schwa]r-si′tis) [*Achilles* + *bursitis*] inflammation and thickening of the bursae about the Achilles tendon, especially of the bursa in front of it; called also *achillodynia*.

achillodynia **(achil·lo·dy·nia)** (ak″[schwa]-lo-din′e-[schwa]) [*Achilles* (tendon) + Gr. *odyn[emacr]* pain + *-ia*] 1. pain in the Achilles tendon. 2. achillobursitis.

achillorrhaphy **(ach·il·lor·rha·phy)** (ak″[schwa]-lor′[schwa]-fe) [*Achilles* (tendon) + Gr. *rhaph[emacr]* suture] suture of the Achilles tendon.

achillotenotomy **(achil·lo·te·not·o·my)** ([schwa]-kil″o-t[schwa]-not′[schwa]-me) [*Achilles* + Gr. *ten[omacr]n* tendon + *tom[emacr]* cut] surgical division of the Achilles tendon.

achroodextrin **(ach·roo·dex·trin)** ([schwa]-kro"o-dek'strin) [*a*-[1] + Gr. *chroa* color + *dextrin*] any of the lower-molecular-weight dextrins not colored by iodine.

Ach |carro's stain **(Ach |·car·ro's stain)** (ah-choo'kah-r[omacr]z) [Nicolús *Ach |carro,* Spanish histologist, 1881–1918] see under stain.

achylia **(achy·lia)** ([schwa]-ki'le-[schwa]) [Gr. *achylos* juiceless + *-ia*] absence of hydrochloric acid and pepsinogens (pepsin) in the gastric juice *(a. gas trica).*

achymia **(achy·mia)** ([schwa]-ki'me-[schwa]) imperfect, insufficient, or absence of formation of chyme.

achymosis **(achy·mo·sis)** (ak"[ibreve]-mo'sis) achymia.

acicular **(acic·u·lar)** ([schwa]-sik'u-l[schwa]r) [L. *acicularis*] shaped like a needle or needle point.

aciculum **(acic·u·lum)** ([schwa]-sik'u-lum) a bent, finger-like spine or bristle found in certain flagellates.

acid **(ac·id)** (as'id) [L. *acidum* from *acidus* sharp, sour] any of a large class of chemical substances defined by three chemical concepts of increasing generality. An *Arrhenius acid* is a substance that lowers the pH (increases the hydrogen ion concentration) when added to an aqueous solution; such substances have a sour taste, turn litmus red, and react with alkalis to form salts. A *Bronsted-Lowry acid* is a species that acts as a proton donor in solution; e.g., the ammonium ion (NH_4^+) can donate a proton leaving ammonia (NH_3); such species are termed conjugate acid-base pairs. A *Lewis acid* is a species that can accept a pair of electrons to form a covalent bond; e.g., BF_3 in the reaction $BF_3 + NH_3 \rightarrow BF_3NH_3$. Aqueous solutions of certain compounds that dissociate in solution, e.g., hydrogen chloride, are designated as acids by names beginning with *hydro-,* e.g., hydrochloric acid. Most other common inorganic acids are *oxo acids* (q.v.); common organic acids include carboxylic acids, sulfonic acids, and phenols. The name of the anion formed by the removal of hydrogen from an acid (its conjugate base) and the names of salts and esters of acids are formed by removing the suffix *-ic* and the word *acid* and adding the suffix *-ate,* except for oxo acids ending in *-ous,* when the suffix is *-ite.* For particular acids, see the specific name.

amino acid, any organic compound containing an amino and a carboxyl group. See amino acid.

binary acid, an acid which contains only two elements, e.g., HCl; called also *hydracid.*

carboxylic acid, any acid containing the carboxyl (—COOH) group, including amino acids and fatty acids.

acid citrate dextrose, (ACD) an anticoagulant solution containing citric acid, sodium citrate, and dextrose formerly used for the preservation of stored whole blood but now primarily for plateletpheresis. Called also *anticoagulant citrate dextrose solution* [USP].

conjugate acid, a chemical species that is formed from its conjugate base by addition of a proton, e.g., ammonium (NH_4^+) is the conjugate acid of ammonia (NH_3).

anticoagulant citrate dextrose solution, [USP] a solution of citric acid, sodium citrate, and dextrose in water for injection, used as an anticoagulant in the preservation of whole blood.

anticoagulant citrate phosphate dextrose solution, [USP] a solution containing citric acid, sodium citrate, sodium biphosphate, and dextrose in water for injection; used for preservation of whole blood or red cells for up to 21 days. Called also *CPD s.*

anticoagulant citrate phosphate dextrose adenine solution, [USP] a solution consisting of anticoagulant citrate phosphate dextrose solution and adenine; used for the preservation of whole blood or red cells for up to 35 days. Called also *CPDA-1 s.* and *CPD-adenine s.*

anticoagulant heparin solution, [USP] a sterile solution of heparin solution in sodium chloride injection, used as an anticoagulant in the preservation of whole blood.

anticoagulant sodium citrate solution, [USP] a solution of sodium citrate in water for injection, used for the storage of whole blood, and for the preparation of citrated human plasma.

heparin **(hep·a·rin)** (hep′[schwa]-rin) [Gr. *h[emacr]par* liver] a sulfated glycosaminoglycan of mixed polysaccharide nature varying in molecular weights and composed of polymers of alternating derivatives of D-glycosamine and L-iduronic acid or D-glucuronic acid; it is released by mast cells and by basophils of the blood and is present in many tissues, especially the liver and lungs. Heparin is a mixture of active principles, some of which have potent anticoagulant properties that result from binding to and greatly enhancing the activity of antithrombin III and from inhibition of a number of coagulation factors, particularly activated factor X (factor Xa). Heparin also has lipotrophic properties, promoting transfer of fat from the blood to the fat depots by activation of lipoprotein lipase.

heparin calcium, [USP] the calcium salt of the mixture of active principles that compose heparin, usually obtained from the intestinal mucosa or other suitable tissues of domestic food animals; used in the prophylaxis and treatment of disorders in which there is undesirable or excessive clotting, such as deep venous thrombosis, thromboembolism, and disseminated intravascular coagulation and to prevent clotting during extracorporeal circulation, blood transfusion, and blood sampling. Administered intravenously or subcutaneously.

heparin sodium, [USP] the sodium salt of the mixture of active principles that compose heparin, usually obtained from the intestinal mucosa or other suitable tissues of domestic food animals, and having the same indications, uses, and routes of administration as the calcium salt.

Haema 2003; 6(3): 407-408
Brief report

A note in the acid citrate dextrose tube in the present usage

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Abstract. Acid citrate dextrose (ACD) is an important blood anticoagulant and preservative. This anticoagulant is mainly used for the blood bank studies, HLA phenotyping, flow cytometry testing, tissue typing, DNA testing. The author reviews the literature on using the ACD vacuum tube in laboratory medicine. ACD is a good blood anticoagulant with few effects on analyses.

Key words: acide citrate dextrose • ACD • anticoagulant

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INTRODUCTION

Acid citrate dextrose (ACD) is an important blood anticoagulant. At present, there are two widely used forms of acid citrate dextrose: namely solution A and solution B. Solution A comprises of 22.0 g/l trisodium citrate, 8.0 g/l citric acid, 24.5 g/l dextrose. Solution B comprises of 13.2 g/l trisodium citrate, 4.8 g/l citric acid, 14.7 g/l dextrose. This anticoagulant is used for the blood bank studies, HLA phenotyping, flow cytometry testing, tissue typing, DNA and paternity testing[1]. It also used as blood preservatives. For the purpose of anticoagulant for further laboratory studies, either solution A or solution B is acceptable. However, for the purpose of blood preservative, solution A is prefered. The action of this additive as anticoagulant is similar to the citrate, resulting in preservation of clotting factor while the dextrose and citric acid make ACD a good red blood cell preservative. Since it contains citrates, therefore, citric acid poisoning (hypocalcaemia) on blood preserved by ACD is mentioned. Symptoms attributable to decrease in calcium ions (numbness in fingers, nausea and, etc.) may occur after massive administration of ACD preserved blood[1]. In addition, ACD is not good medium for rheology studies, as it cause deformability of stored erythrocytes, resulting in bad filterability[2].

In this article, the author reviews on the usage of it as anticoagulant. At present, the ACD is another application in the evacuated blood collection system, the widely used blood collection technique. Concerning the order of drawn the ACD tube should be set as the last tube (Table 1). Both solution A (8 ml draw) and solution B (3 ml draw) ACD vacuum tube is available but the solution A tube is larger.

LITERATURE ON USING ACD TUBE IN LABORATORY MEDICINE

ACD Anticoagulant Effect on Clotting Factor and Platelet

The ACD is claimed to be a good blood anticoagulant, which can preserve the clotting factors. Lombarts and de Kieviet[3] reported that ACD vacuum tube can prevent unrecognized anticoagulant - induced

Table 1. Order of drawn.

Order	Tube	Stopper color
1.	Trace metal free tube with EDTA	Navy blue
2.	Sterile tube without additive	Pink
3.	Citrate tubes for coagulation tests	Light blue
4.	Gel (SST) tube with clot activator	Tiger
5.	Sodium-heparin tube without gel	Green
6.	Lithium-heparin tube with gel	Lime green
7.	EDTA tube	Purple
8.	Oxalate/fluoride tube	Gray
9.	Acid-Citrate Dextrose tube	Yellow

platelet aggregation, leading to pseudothrombocytopenia and concomitant pseudoleukocytosis, which EDTA and heparin generally induce. Pignatelli et al studied on the storage on in vitro platelet responses comparing to sodium citrate anticoagulant[4]. They concluded that the use of ACD Formula A as anticoagulant is capable of maintaining a normal platelet responsiveness up to 6-8 hours, thus permitting the investigation of platelet function for periods of time over those commonly recommended. Pignatelli et al also performed another study to evaluate whether the use of ACD Formula A may affect in vitro platelet function. They found that the ACD treated platelets showed a higher reactivity to the agonists as demonstrated by a significant increase of the maximum percentages of aggregation induced by ADP, epinephrine, and collagen, as well as a significant decrease of secondary aggregation thresholds to ADP and epinephrine[5]. From this study, it may be speculated that ACD Formula A is capable of better maintaining the intraplatelet signal transduction mechanisms during PRP preparation, thus improving the overall responsiveness of platelets[5].

ACD Anticoagulant Effect on Virology Test

ACD has been shown to display no significant difference of virology test comparing to the standard EDTA anticoagulant. Fiscus et al studied blood samples collected in acid-citrate-dextrose and EDTA for human immunodeficiency virus (HIV) infectivity on the day of collection or after 1 day of storage at room temperature. According to this study, no significant differences between the anticoagulants were observed. Culture positivity was significantly associated with HIV RNA viral loads for both anticoagulants[6]. Similar study from Landry et al on cytomegalovirus (CMV) virology test was performed. In this study, duplicate blood samples collected in EDTA and ACD were compared by CMV pp65 antigenaemia and CMV infectivity on the day of sample collection and after 1 and 2 days of storage at 4°C. Interestingly, no significant difference was detected between EDTA and ACD[7].

ACD Anticoagulant Effect on Leukocyte

ACD anticoagulant is believed to be a good anticoagulant for leukocyte preservation. Comparison of heparin and ACD as anticoagulants revealed that ss-glucuronidase and hexosaminidase activities in plasma reached levels near the lower normal limits when ACD was used[8].

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